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| CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110 | | | CAPPs, KEVIN J | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/518,689 | GUARNA ET AL. | |
| | Examiner | Art Unit | |
| | Kevin Capps | 1617 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 31 January 2007.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 22-42 is/are pending in the application.
- 4a) Of the above claim(s) 27-40 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 22-26, 41, and 42 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All
 - b) Some *
 - c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____. | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Status of the Claims

1. This Office Action is in response to the Remarks and Amendments filed on January 31, 2007. Claims 22-42 are pending. Claims 22-26, 41, and 42 are examined on the merits herein to the extent that they read on the elected invention of compounds of general formula (I) and pharmaceutical compositions comprising said compounds.
2. In view of Applicant's correction of informalities in claim 25, the objection is withdrawn.
3. Claim 41 stands rejected under 35 U.S.C. 102(b) as being anticipated by Van Cauwenberghe et al. (Van Cauwenberghe et al. *Heterocycles* **1975**, 3, 101-107). In view of Applicant's amendments disclaiming the compounds disclosed in the reference, the rejection is withdrawn.
4. Claim 41 stands rejected under 35 U.S.C. 102(b) as being anticipated by May et al. (Applicant-cited reference on IDS: May et al. *J. Pharmaceutical Sciences* **1968**, 57, 511-513). In view of Applicant's amendments disclaiming the compounds disclosed in the reference, the rejection is withdrawn.
5. Claim 41 stands rejected under 35 U.S.C. 102(b) as being anticipated by Guidi et al. (Guidi et al. *Arch. Pharm. Pharm. Med. Chem.* **1997**, 330, 201-202). In view of Applicant's amendments disclaiming the compounds disclosed in the reference, the rejection is withdrawn.

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6. Claim 41 stands rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al. (Wang et al. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 1, 209-212). In view of Applicant's amendments disclaiming the compounds disclosed in the reference, the rejection is withdrawn.

7. Claims 22-24, 26, and 41 stand rejected under 35 U.S.C. 102(b) as being anticipated by Guerret et al. (US 4,463,004). In view of Applicant's amendments to claim 41 disclaiming the compounds disclosed in the reference, the rejection is withdrawn for this claim. The rejection is maintained, however, for claims 22-24 and 26, and restated below to address Applicant's claim amendments. Applicant's arguments are addressed below.

8. Claim 41 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Van Cauwenberghe et al. (Van Cauwenberghe et al. *Heterocycles* **1975**, 3, 101-107). The rejection is withdrawn for the reasons set forth below in the Response to Arguments.

9. Claim 41 stands rejected under 35 U.S.C. 103(a) as being unpatentable over May et al. (Applicant-cited reference on IDS: May et al. *J. Pharmaceutical Sciences* **1968**, 57, 511-513). The rejection is withdrawn for the reasons set forth below in the Response to Arguments.

10. Claim 41 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Guidi et al. (Guidi et al. *Arch. Pharm. Pharm. Med. Chem.* **1997**, 330, 201-202). The rejection is maintained. Applicant's arguments are addressed below.

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11. Claim 41 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (*Wang et al. J. Chem. Soc., Perkin Trans. 1, 1996, 1, 209-212*). The rejection is withdrawn for the reasons set forth below in the Response to Arguments.

12. Claims 22-24, 26, and 41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Guerret et al. (US 4,463,004). The rejection is maintained. Applicant's arguments are addressed below.

13. Claims 41 and 42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (WO 01/64686). The rejection is maintained. Applicant's arguments are addressed below.

14. Claims 41 and 42 stand rejected under 35 U.S.C. 103(a) as being obvious over Guarna et al. (US 2003/0176414). The rejection is maintained. Applicant's arguments are addressed below.

15. Claims 22-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (WO 01/64686). The rejection is maintained. Applicant's arguments are addressed below.

16. Claims 22-26 stand rejected under 35 U.S.C. 103(a) as being obvious over Guarna et al. (US 2003/0176414). The rejection is maintained. Applicant's arguments are addressed below.

17. Claim 41 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (*Guarna et al. Tetrahedron: Asymmetry 2000, 11, 4227-4238*). The rejection is maintained. Applicant's arguments are addressed below.

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18. Claims 41 and 42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Scarpi et al. (Scarpi et al. *Bioorg. Med. Chem.* **2001**, 9, 1625-1632). The rejection is maintained. Applicant's arguments are addressed below.

19. Claims 41 and 42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Machetti et al. (Applicant-cited reference on IDS: Machetti et al. *Org. Lett.* **2000**, 2, 3987-3990). The rejection is maintained. Applicant's arguments are addressed below.

20. Claims 22-26, 41, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (Applicant-cited reference on IDS: Guarna et al. *J. Org. Chem.* **1999**, 64, 7347-7364). The rejection is maintained. Applicant's arguments are addressed below.

21. Claims 22-26, 41, and 42 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of copending Application No. 10/220,556. The rejection is maintained. Applicant's arguments are addressed below.

Claim Rejections - 35 USC § 112

22. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. Claim 41 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

24. Applicant's newly added negative limitations excluding compounds disclosed in the prior art do not have basis in the instant specification. See MPEP 2173.05(i), which states: "Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims", and, "Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement." See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) and *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983).

25. Applicant points to p. 3, ll. 13-16, p. 24, ll. 5-11, and p. 2, l. 11-p. 4, l. 9 for support of the new negative limitations in claim 41 (p. 28 of Remarks). However, nowhere in these sections is there a positive recitation of the specific substituents that are now excluded. For example, Applicant has amended claim 41 to exclude a compound wherein $R_6 = CH_2NMe_2$. However, nowhere in the specification is this specific substituent positively recited. The only reference to R_6 in the sections referred to by Applicant relating to this substituent is to CH_2NRR' , wherein R and R' can be, among many other things, alkyl. Therefore, there is no basis in the specification for excluding $R_6 = CH_2NMe_2$ from the claims. This analysis holds true for many of the specific substituents that are now excluded from the claim, but are not positively recited in the specification.

Claim Rejections - 35 USC § 102

26. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

27. Claims 22-24 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Guerret et al. (US 4,463,004).

28. Guerret et al. teach compounds within the scope of the instant formula (I) wherein X is H, Y and Z are O, R₂, R₄, R₅, and R₆ are H, R₁ is H, alkyl having at least 4 carbons, cyclohexyl, or aryl, and R₃ is C₁ to C₄ alkyl, cyclohexyl, or benzyl (claim 1; Table I). Many compounds within the scope of the instant formula (I) are exemplified (see compounds 18, 37, and 43 in Table I, for example). Guerret et al. teach that the compounds have “pharmacological properties”, particularly “analgesic activity” (col. 17, lines 12-56). Guerret et al. teach preparation of the compounds as pharmaceutical compositions for administration as analgesics (col. 17, line 57-col. 18, line 15).

29. Although Guerret et al. do not disclose the use of the compositions for the treatment of diseases involving defective neurotrophine function, the intended use does not distinguish the instantly claimed compositions from those disclosed by Guerret et al. because it does not result in a structural difference. In other words, the compositions of Guerret et al. inherently meet the instantly claimed intended use. See MPEP § 2111.02 (II). Thus, Guerret et al. anticipate the instantly claimed inventions.

Claim Rejections - 35 USC § 103

30. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

31. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

32. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guidi et al. (Guidi et al. *Arch. Pharm. Pharm. Med. Chem.* **1997**, 330, 201-202.).

33. Guidi et al. teach the compound of formula (I) wherein X, Y, and Z are O, R₁, R₄, and R₅ are H, R₂ and R₃ are aryl C₁ alkyl, and R₆ is C(O)OR, wherein R is C₁ alkyl (see compound 3 on p. 201). In the introduction, Guidi et al. discuss the use of the compounds as peptidomimetic scaffolds for use "either for recognition purposes or for discovering new drugs." (p. 201). Thus, Guidi et al. teach a pharmacological utility of the compounds.

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34. Guidi et al. do not teach compounds of formula (I) wherein X, Y, and Z are O, R₁, R₄, and R₅ are H, R₂ and R₃ are aryl alkyl with alkyl greater than C₁, and R₆ is C(O)OR, wherein R is greater than C₁ alkyl.

35. Adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed by the prior art. *In re Hass*, 141 F.2d 127, 60 USPQ 548 CCPA 1944. Thus, the person of ordinary skill in the art would have been motivated to make the compounds of Guidi et al. wherein R₂ and R₃ are aryl alkyl with alkyl greater than C₁, and R₆ is C(O)OR, wherein R is greater than C₁ alkyl, with a reasonable expectation of success because adjacent homologs are expected to possess similar pharmacological properties. See MPEP § 2144.09.

36. Although Guidi et al. do not disclose use of the compounds for the treatment of diseases involving defective neurotrophine function, the reference provides motivation to make the instantly claimed compounds with the expectation that they would possess similar properties to those disclosed by Guidi et al. See MPEP § 2144.09, which states, "a claimed compound may be obvious because it was suggested by, or structurally similar to, a prior art compound even though a particular benefit of the claimed compound asserted by patentee is not expressly disclosed in the prior art...If the prior art compound does in fact possess a particular benefit, even though the benefit is not recognized in the prior art, applicant's recognition of the benefit is not in itself sufficient to distinguish the claimed compound from the prior art."

37. Claims 22-24, 26, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guerret et al. (US 4,463,004).

38. Guerret et al. teach compounds of the instant formula (I) wherein X is H, Y and Z are O, R₂, R₄, R₅, and R₆ are H, R₁ is H, alkyl having at least 4 carbons, cyclohexyl, or aryl, R₃ is C₁ to C₄ alkyl, cyclohexyl, or benzyl (claim 1; Table I). Guerret et al. teach that the compounds have "pharmacological properties", particularly "analgesic activity" (col. 17, lines 12-56). Guerret et al. teach preparation of the compounds as pharmaceutical compositions for administration as analgesics (col. 17, line 57-col. 18, line 15).

39. Guerret et al. do not teach compounds of the instant formula (I) wherein X is H, Y and Z are O, R₂, R₄, R₅, and R₆ are H, R₁ is alkyl having less than 4 carbons, and R₃ is greater than C₄ alkyl.

40. For the reasons discussed above, the person of ordinary skill in the art would have been motivated to make the compounds of Guerret et al. wherein R₁ is alkyl having less than 4 carbons or R₃ is greater than C₄ alkyl with a reasonable expectation of success because adjacent homologs are expected to have similar properties.

41. Although Guerret et al. do not disclose use of the compounds for the treatment of diseases involving defective neurotrophine function, the reference provides motivation to make the instantly claimed compounds with the expectation that they would possess similar properties to those disclosed by Guerret et al. See MPEP § 2144.09, which states, "a claimed compound may be obvious because it was suggested by, or structurally similar to, a prior art compound even though a particular benefit of the

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claimed compound asserted by patentee is not expressly disclosed in the prior art...If the prior art compound does in fact possess a particular benefit, even though the benefit is not recognized in the prior art, applicant's recognition of the benefit is not in itself sufficient to distinguish the claimed compound from the prior art."

42. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (WO 01/64686).

43. Guarna et al. teach the instant compounds 138 and 142 with undefined stereochemistry (see compound 214 on p. 43). Guarna et al. teach use of the compounds "for the discover [sic] of new leads for therapeutical applications." (p. 3, II.. 9-11).

44. Guarna et al. do not teach the resolved stereoisomers of compound 214, i.e., the instantly claimed compounds 138 and 142.

45. The expectation with regard to stereoisomers is that activities as they pertain to living systems are expected to be different. *In re Adamson*, 275 F.2d 952, 125 USPQ 233 (CCPA 1960). The fundamentals of optical activity and stereoisomerism are well known to persons having ordinary skill in the art. A person having ordinary skill in the art would have known how to resolve the racemic mixture and would have been motivated to do so with the reasonable expectation of achieving stereoisomers having substantially different pharmacological activity. Thus, the instantly claimed stereoisomers of compound 214 in Guarna et al. would have been obvious to the person of ordinary skill in the art at the time of invention.

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46. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being obvious over Guarna et al. (US 2003/0176414).

The applied reference has a common inventor with the instant application.

Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

47. This US application is the national stage entry of the international application published as WO 01/64686. Therefore, the basis of this rejection is the same as that stated above.

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48. Claims 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (WO 01/64686).

49. Guarna et al. teach the instant compounds 138 and 142 with undefined stereochemistry and their use for discovering new therapeutic agents (see compound 214 on p. 43). As discussed above, the instantly claimed resolved stereoisomers of the compounds of Guarna et al. are *prima facie* obvious.

50. It would have been obvious to the person of ordinary skill in the art to formulate the compounds of Guarna et al. with pharmaceutically acceptable excipients in a pharmaceutical composition to arrive at the instantly claimed invention.

51. The person of ordinary skill in the art would have been motivated to formulate the compounds of Guarna et al. with pharmaceutically acceptable excipients as a pharmaceutical composition because Guarna et al. teach that the compounds are intended for therapeutic applications. The person of ordinary skill in the art would have expected that the compounds could be formulated with routinely used, pharmaceutically acceptable excipients because this is a routine practice in the art for administering therapeutic agents.

52. Claims 22-26 are rejected under 35 U.S.C. 103(a) as being obvious over Guarna et al. (US 2003/0176414).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome

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by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(I)(1) and § 706.02(I)(2).

53. This US application is the national stage entry of the international application published as WO 01/64686. Therefore, the basis of this rejection is the same as that stated above.

54. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (Guarna et al. *Tetrahedron: Asymmetry* **2000**, *11*, 4227-4238.).

55. Guarna et al. teach the instant compounds 34, 58, and 176, as defined in claim 25 (see compounds 11-13 on p. 4230). As acknowledged by Applicant in the latest Remarks, Guarna et al. teach use of the compounds as chiral auxiliaries (p. 41 of Remarks).

56. Guarna et al. do not teach the instant compounds 35, 59, or 177, as defined in claim 25, which are stereoisomers of the above-cited compounds.

57. The person of ordinary skill in the art would have been motivated to prepare the instantly claimed enantiomers of the compounds disclosed in Guarna et al. because they could be used for the same purpose (i.e., as chiral auxiliaries) to prepare opposite enantiomers of the compounds prepared in Guarna et al. The person of ordinary skill in the art would have expected success because they would understand that if the chiral auxiliaries of Guarna et al. can be used to give a certain stereochemistry of a product, then the opposite enantiomer of the auxiliary could be used to prepare the opposite enantiomer of the product.

58. Although Guarna et al. do not disclose use of the compounds for the herein-claimed function, the reference provides motivation to make the instantly claimed compounds with the expectation that they would possess similar properties to those disclosed by Guarna et al. See MPEP § 2144.09, which states, "a claimed compound may be obvious because it was suggested by, or structurally similar to, a prior art compound even though a particular benefit of the claimed compound asserted by patentee is not expressly disclosed in the prior art...If the prior art compound does in fact possess a particular benefit, even though the benefit is not recognized in the prior art, applicant's recognition of the benefit is not in itself sufficient to distinguish the claimed compound from the prior art."

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59. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scarpi et al. (Scarpi et al. *Bioorg. Med. Chem.* **2001**, 9, 1625-1632.).

60. Scarpi et al. teach the instant compound 32, as defined in claim 25 (see compound 1 on p. 1627). Scarpi et al. disclose incorporation of the compound into a peptide as a dipeptide isostere, as well as the biological properties of the peptide comprising the compound (Figure 3; p. 1630).

61. Scarpi et al. do not teach the instant compound 33, as defined in claim 25, which is a stereoisomer of the instant compound 32.

62. The person of ordinary skill in the art would have been motivated to make the instantly claimed enantiomer of compound 1 in Scarpi et al. because the compound could also be used as a dipeptide isostere in the peptides. The person of ordinary skill in the art would have expected that the compound could be used as a dipeptide isostere in the peptides because there is nothing about inverting the stereochemistry of the compound that would preclude its incorporation into a peptide.

63. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Machetti et al. (Applicant-cited reference on IDS: Machetti et al. *Org. Lett.* **2000**, 2, 3987-3990.).

64. Machetti et al. teach the instant compound 36, as defined in claim 25 (see compound 1 on p. 1627). Machetti et al. disclose use of the compounds in the form of oligomers as catalysts and artificial enzymes and receptors (pp. 3987-3988).

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65. Machetti et al. do not teach the instant compound 37, as defined in claim 25, which is a stereoisomer of the instant compound 36.

66. The person of ordinary skill in the art would have been motivated to prepare the instantly claimed stereoisomers of the compounds of Machetti et al. because the compounds would be expected to useful as catalysts for the opposite configuration of products.

67. Claims 22-26, 41, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (Applicant-cited reference on IDS: Guarna et al. *J. Org. Chem.* **1999**, *64*, 7347-7364.).

68. Guarna et al. teach compounds within the scope of the instant genus of compounds comprising the 3-aza-bicyclo[3.2.1]octane core, as well as specific compounds defined in the instant claim 25. For example, Guarna et al. teach compound 192 of the instant claim 25, which is the compound of the instant formula (I) wherein X, Y, and Z are O, R₁, R₄, and R₅ are H, R₂ is (S)-Me (C₁ alkyl), R₃ is C₁ arylalkyl, and R₆ is (R)-C(O)OR, wherein R is C₁ alkyl (see compound 12 on p. 7353). Guarna et al. teach a general strategy for preparing all of the individual stereoisomers of the compounds comprising the 3-aza-bicyclo[3.2.1]octane core (see Chart 1 on p. 7349). Guarna et al. teach, "Peptide isosteres are compounds that can replace one or more amino acids in a bioactive peptide leading to modified structures possibly displaying more favorable pharmacological properties than the prototype. In several cases, the modified peptide shows a higher metabolic stability, better bioavailability, and

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higher receptor affinity or selectivity." (p. 7347). Guarna et al. go on to discuss five properties of peptide isosteres that would achieve these desired pharmacological properties. Guarna et al. state, "We have envisioned that some of...these features could be found in the bicyclic structure based upon 3-aza-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic acid skeleton". Thus, Guarna et al. suggest the pharmaceutical utility of compounds comprising the 3-aza-bicyclo[3.2.1]octane core

69. Guarna et al. do not explicitly teach the instant compounds 193-195 as defined in claim 25, which are stereoisomers of compound 192 of the instant claim 25. Guarna et al. do not teach compounds of formula (I) wherein X, Y, and Z are O, R₁, R₄, and R₅ are H, and wherein R₂ is alkyl greater than C₁, or R₃ is aryl alkyl with alkyl greater than C₁, or R₆ is C(O)OR, wherein R is greater than C₁ alkyl. Guarna et al. do not teach preparation of pharmaceutical compositions comprising the herein-claimed compounds comprising the 3-aza-bicyclo[3.2.1]octane core.

70. For the reasons discussed above, the herein-claimed stereoisomers of the compounds disclosed by Guarna et al. are *prima facie* obvious, particularly considering that Guarna et al. teach a general strategy for preparing all of the possible stereoisomers. For the reasons discussed above, the herein-claimed adjacent homologs and homologous series are *prima facie* obvious. Because Guarna et al. suggest the pharmaceutical utility of the herein-claimed compounds comprising the 3-aza-bicyclo[3.2.1]octane core, it would have been obvious to the person of ordinary skill in the art to formulate the compounds with pharmaceutically acceptable excipients to arrive at the instantly claimed inventions.

71. The person of ordinary skill in the art would have been motivated to formulate the compounds of Guarna et al. with pharmaceutically acceptable excipients as a pharmaceutical composition because Guarna et al. teach that the compounds have pharmaceutical utility, and bioactive compounds are routinely formulated as pharmaceutical compositions for administration in therapeutic methods. The person of ordinary skill in the art would have expected that the compounds could be formulated with routinely used, pharmaceutically acceptable excipients absent evidence to the contrary.

Double Patenting

72. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

73. Claims 22-26, 41, and 42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of copending Application No. 10/220,556. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds of '556 either overlap in scope or are within the scope of the instantly claimed compounds. Further, the instantly claimed pharmaceutical compositions are obvious in view of '556. The Patent Application Publication for this application (US 2003/0176414) was the basis of the 35 USC § 103 rejections set forth above. Therefore, the reasoning for this rejection is the same as that set forth above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

74. Regarding the rejection of claims 22-24 and 26 under 35 U.S.C. 102(b) as being anticipated by Guerret et al. (US 4,463,004), Applicant argues that the pharmaceutical compositions of Guerret et al. are used as analgesics, whereas the instantly claimed pharmaceutical formulations are for "the treatment of diseases in which neurotrophine functions are involved in defect." However, as discussed above, the intended use does not distinguish the instantly claimed compositions from those disclosed by Guerret et al. because it does not result in a structural difference. See MPEP § 2111.02 (II).

75. Regarding the rejection of claim 41 under 35 U.S.C. 103(a) as being unpatentable over Van Cauwenberghe et al. (Van Cauwenberghe et al. *Heterocycles*

1975, 3, 101-107), Applicant argues that the instantly claimed adjacent homologues of the compound in Van Cauweberghe et al. are not *prima facie* obvious because of the unexpected result that the compounds “possess an unexpected pharmacological activity, e.g., as neutrophine agonists” (p. 32 of Remarks). However, if Van Cauweberghe et al. provide motivation to prepare the instantly claimed adjacent homologues, this is sufficient to reject the compounds under § 103. See MPEP § 2144.09, which states, “a claimed compound may be obvious because it was suggested by, or structurally similar to, a prior art compound even though a particular benefit of the claimed compound asserted by patentee is not expressly disclosed in the prior art...If the prior art compound does in fact possess a particular benefit, even though the benefit is not recognized in the prior art, applicant’s recognition of the benefit is not in itself sufficient to distinguish the claimed compound from the prior art.” The rejection is withdrawn, however, not in view of Applicant’s arguments concerning the newly discovered utility of the compounds, but because Van Cauweberghe et al. do not teach utility of the compounds, and thus do not provide motivation to prepare the herein-claimed adjacent homologues. See MPEP § 2144.09, which states, “If the prior art does not teach any specific or significant utility for the disclosed compounds, then the prior art is not sufficient to render structurally similar claims *prima facie* obvious because there is no motivation for one of ordinary skill in the art to make the reference compounds, much less any structurally related compounds.”

76. Similarly, the rejections of claim 41 under 35 U.S.C. 103(a) as being unpatentable over May et al. (Applicant-cited reference on IDS: May et al. J.

Pharmaceutical Sciences **1968**, 57, 511-513) and also under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (Wang et al. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 1, 209-212) are withdrawn because the references do not disclose a utility of the parent compounds of the instantly claimed adjacent homologues, and thus do not provide motivation to prepare the herein-claimed adjacent homologues.

77. Regarding rejection of claim 41 under 35 U.S.C. 103(a) as being unpatentable over Guidi et al. (Guidi et al. *Arch. Pharm. Pharm. Med. Chem.* **1997**, 330, 201-202), Applicant argues that the instantly claimed compounds possess "an unexpected pharmacological activity, e.g., as neurotrophine agonists" (p. 34 of Remarks). However, as stated above, Guidi et al. teach utility of the compounds, which, as discussed above, provides sufficient motivation to prepare the instantly claimed adjacent homologues.

78. Regarding the rejection of claims 22-24, 26, and 41 under 35 U.S.C. 103(a) as being unpatentable over Guerret et al. (US 4,463,004), Applicant argues that the instantly claimed compounds and compositions containing them "possess an unexpected neurotrophine agonist activity", and that the compositions have been claimed with this intended use. However, Guerret et al. disclose pharmaceutical utility of the compounds, albeit different than that disclosed by Applicant, thus providing motivation to prepare the instantly claimed compounds and compositions. See MPEP § 2144.09, which states, "If the prior art does not teach any specific or significant utility for the disclosed compounds, then the prior art is not sufficient to render structurally similar claims *prima facie* obvious because there is no motivation for one of ordinary skill in the art to make the reference compounds, much less any structurally related compounds."

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Further, the intended use of the instantly claimed compositions does not distinguish them from those that are obvious from Guerret et al. because it does not result in a structural difference.

79. Regarding the rejections of claims 41 and 42 under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (WO 01/64686), claims 41 and 42 under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (US 2003/0176414), claims 22-26 under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (WO 01/64686), claims 22-26 under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (US 2003/0176414), claim 41 under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (Guarna et al. *Tetrahedron: Asymmetry* 2000, 11, 4227-4238), claims 41 and 42 under 35 U.S.C. 103(a) as being unpatentable over Scarpi et al. (Scarpi et al. *Bioorg. Med. Chem.* 2001, 9, 1625-1632), and claims 41 and 42 under 35 U.S.C. 103(a) as being unpatentable over Machetti et al. (Applicant-cited reference on IDS: Machetti et al. *Org. Lett.* 2000, 2, 3987-3990), Applicant has presented arguments relating to the non-obviousness of adjacent homologues. However, this was not the basis of the rejections. The rejections concern the obviousness of claimed stereoisomers of known compounds. Therefore, Applicant's arguments do not relate to the outstanding rejections.

80. Regarding the rejection of claims 22-26, 41, and 42 under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (Applicant-cited reference on IDS: Guarna et al. *J. Org. Chem.* 1999, 64, 7347-7364), Applicant again argues that the instantly claimed

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compounds and compositions possess activity not disclosed in the art. This line of argumentation has been addressed above.

81. Applicant argues that the provisional obviousness-type double patenting rejection should be withdrawn for the reasons presented against the § 103 rejection over Guarna et al. (US 2003/0176414). Therefore, the rejection is maintained for the reasons stated above.

Conclusion

82. No claims are allowed.

83. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin Capps whose telephone number is (571) 272-8646. The examiner can normally be reached on Monday-Friday, 7:30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KC



SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER